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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/029,304	12/28/2001	Jonathan A. Ellman	045413/0110	3985

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EXAMINER	
EPPERSON, JON D	
ART UNIT	**PAPER NUMBER**
1639	

DATE MAILED: 11/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	10/029,304	ELLMAN ET AL.	
	Examiner	Art Unit	
	Jon D Epperson	1639	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.
2. ☐ The proposed amendment(s) will not be entered because:
   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ they raise the issue of new matter (see Note below);
   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.
   NOTE: _____.
3. ☐ Applicant's reply has overcome the following rejection(s): _____.
4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *Please see attached shet*.
6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.
7. ☒ For purposes of Appeal, the proposed amendment(s) a)☒ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: *34,53,54 and 58*.

   Claim(s) withdrawn from consideration: *35-37, 55-57 and 59*.
8. ☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.
9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.
10. ☐ Other: _____

DETAILED ACTION

Status of the Application

1. The After-Final Response filed August 24, 2004 is acknowledged and Applicants' arguments are addressed below.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of the Claims

3. Claims 34-37 and 53-59 were pending. Applicants did not amend, add or cancel any claims. Therefore, claims 34-37 and 53-59 are still currently pending.

4. Claims 35-37, 55-57 and 59 are drawn to non-elected species and/or inventions and thus these claims remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b), there being no allowable generic claim.

5. Therefore, claims 34, 53, 54 and 58 are currently active.

Maintained Rejections

Claims Rejections - 35 U.S.C. 102

6. Claims 34 is rejected under 35 U.S.C. 102(e) as being anticipated by Wells et al. (US Patent No. 6,335,155) (Filing Date is **June 26, 1998**).

For ***claim 34***, Wells et al. (see entire document) disclose libraries that are used in methods for rapidly identifying organic molecule ligands for binding to biological target molecules (see Wells et al., abstract), which anticipates claim 34. For example, Wells et al. disclose a library of candidate target binding fragments wherein said fragments are small organic molecules (e.g., see abstract, see also claim 1, "combining said biological target molecule with one or more members of a library of small, non-oligomeric soluble, synthetic organic ligand candidates"). Wells et al. also disclose library members with a disulfide-linking group (e.g., see claim 1; see also column 3, "Other embodiments of the above described methods employ libraries of organic compounds which comprise ... disulfides"; see also column 3, last paragraph; see also column 8, paragraph 3; see also column 10, line 46; see also column 16, first full paragraph). Finally, Wells et al. disclose mixing a least two candidate target binding molecules together (e.g., see column 11, paragraph 1, "Libraries of organic compounds which find use herein will generally comprise at least 2 organic compounds, often at least about 25 different organic compounds ... preferably at least about 5000 or more different organic compounds"; see also claim 1 step (b), "combining [i.e., mixing] said biological target molecule with one or more members of a library").

Response

7. Applicant's arguments directed to the above 35 U.S.C. § 102 rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed

persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

Applicants argue, "... that their priority claim to US Application No. 09/049,754, now US Patent No. 6,344,330 ('US '330), precludes the use of Wells as a prior art reference" (e.g., .

This is not found persuasive for the following reasons:

The Examiner contends that Applicants priority date for 09/049,754 has not been granted and, as a result, Applicants' arguments are moot. The Examiner cannot find support for the blocked form of candidate target binding fragments. If applicant believes this rejection is in error, applicant must disclose where in the specification support for this amendment can be found in accordance with MPEP 714.02 (e.g., the recited passages do not mention this limitation). In addition, the Examiner does not find support for the full scope of "candidate target binding fragments" in the passages cited by Applicants because said "fragments" include both "ligands" and "non-ligands" whereas the '330 patent only provides support for tethering "ligands" that bind to the target molecule (i.e., molecules that can bind to the target molecule on their own without the assistance of another tethered molecule).

Accordingly, the 35 U.S.C. 102 rejection cited above is hereby maintained.

Claim Rejections - 35 USC § 103

8. Claims 34, 53 and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kirkpatrick et al. (U.S. Patent 6,552,060) (Filing Date is **August 11, 1998**) and Konings et al. (Konings, D. A. M.; Wyatt, J. R.; Ecker, D. J.; Freier, S. M. "Deconvolution of Combinatorial

Libraries for Drug Discovery: Theoretical Comparison of Pooling Strategies" *J. Med. Chem.* **1996**, *39*, 2710-2719).

For ***claims 34, 53 and 54***, Kirkpatrick et al. (see entire document) disclose a library of at least two disulfides with the formula CTBF-S-S-R^8 wherein R^8 is a straight chain alkyl or branched aminoalkyl or hydroxyalkyl (e.g., see figure 5; see also figures 9-11, especially figure 10 wherein R'=A, B, C, D, M and O; see also paragraph bridging columns 4-5; Table 3, especially compounds F-27, M-13 and M-29; see also column 22; see especially claims 8 and 19 wherein R^8 represents branched alkyls substituted with amino or hydroxy groups; see also column 4, last paragraph wherein n-butyl imidazolyl disulfide is disclosed; see also column 5, line 5 wherein a straight chain hydroxyalkyl is disclosed) and the CTBF (i.e., the candidate target binding fragment) binds to, for example, thioredoxin reductase/thioredoxin targets (e.g., see figure 5; see also columns 7-11).

The prior art teachings of Kirkpatrick et al differ from the claimed invention as follows:

For ***claims 34, 53 and 54***, Kirkpatrick et al. do not teach a "mixture" of library members. Kirkpatrick et al. teach contacting the library members "separately" using a microtiter plate (i.e., "one compound per one well") for screening purposes (e.g., see Kirkpatrick et al., column 22, paragraph 1, "Using a 96 well plate [i.e., a microtiter plate] format, parallel combinatorial chemistry ... was used to synthesize a large number of unsymmetrical disulfides"; see also column 23, paragraph 1, "A second plate [i.e.,

microtiter plate] was used for the assessment of biological activity or as a biological screen [i.e., parallel screening using a microtiter plate]").

However, Konings et al. teach the following limitations that are deficient in Kirkpatrick et al.:

For ***claims 34, 53 and 54***, Konings et al. (see entire documents) teach the use of a "mixture" of library members wherein the reaction and/or screening is carried out in one reaction vessel instead of using separate vessels and/or separate wells of a microtiter plate. For example, Konings et al. state, "[s]ynthesis and testing of mixtures of compounds [referred to herein as mixing technology] in a combinatorial library allow much greater throughput than synthesis and testing of individual compounds [e.g., individual synthesis and/or screening using microtiter plates]" (e.g., see Konings et al. abstract) and also state that this mixing technology is generally applicable to a "variety of chemistries" (e.g., see Konings et al. page 2710, column 1, paragraph 2; see also figure 2 wherein the screening of a library of 27 compounds is shown), which would include the disulfide libraries of Kirkpatrick et al.

Therefore, it would have been *prima facie* obvious to one of ordinary skill to create and/or screen a library as disclosed by Kirkpatrick et al. using the "mixing" technology as taught by Konings et al. because the method of forming and/or screening a library (e.g., microtiter plates versus "mixing" technology) represents a mere design choice (i.e., both methods were well known in the art at the time of filing and could be used interchangeably to produce and/or screen libraries of organic compounds). A person of ordinary skill in the art would have been motivated to use the "mixing

technology" as exemplified by Konings et al. to create and/or screen a larger number of compounds in a shorter period of time than could be achieved using the "one compound, one well" approach employed by Kirkpatrick et al. (e.g., see Konings et al., page 2710, column 1, paragraph 1, "Synthesis and testing of mixtures of compounds in a combinatorial library offer the potential of much greater throughput than the 'one compound, one well' approach" i.e., use of microtiter plate; see also abstract). Furthermore, a person of ordinary skill in the art would have had a reasonable expectation of success because Konings et al. state that the method is generally applicable to all compounds (e.g., see Konings et al., page 2710, column 1, paragraph 2), which would include the disulfide structures disclosed by Kirkpatrick et al.

Response

9. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue, "As a result of the complexities of identifying compounds that affect the thioredoxin/thioredoxin reductase enzymes, one of skill in the art would not have been motivated to assay a mixture of asymmetrical disulfide compounds against this system" (e.g., see 8/24/04 Response, pages 3-5, especially page 5, first full paragraph).

[2] Applicants argue that there would be no reasonable expectation of success because different molecular interactions are occurring in the two references (e.g., see 8/24/04 Response, pages 5-6).

This is not found persuasive for the following reasons:

[1] In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., asymmetrical disulfide compounds) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

In addition, the Examiner notes that Applicants have not provided any evidence to support the position that the disulfide compounds could not be easily analyzed in this system. The Examiner contends that many routine techniques including NMR, mass-spec and various combinatorial deconvolution techniques could be employed.

[2] The Examiner respectfully disagrees. The application of combinatorial techniques does not depend upon the type of interaction employed and, as a result, Applicants' arguments are moot (e.g., see Konings et al., page 2710, column 1, paragraph 2 wherein they state that the method is generally applicable to all compounds, which would include the disulfide structures disclosed by Kirkpatrick et al).

Applicants further argue that Konings et al. cannot be read as broadly as the Examiner contends where "all compounds" are encompassed. Again, the Examiner respectfully disagrees. Combinatorial chemistry is a well-established field and has been applied to virtually every area of chemistry without limit. The Examiner sets forth the table of contents of Nicolaou et al. (see

Nicolaou, K. C.; Hanko, R.; Hartwig, W. Eds. in "Handbook of Combinatorial Chemistry" Weinheim Germany: Wiley-VCH 2002, Vol. 1, page v-xxv) for the sole purpose of rebutting Applicants' arguments that such techniques would only be narrowly applied to exclude any of the compounds sets forth in Kirkpatrick. The Examiner further notes that Applicants' have not provided any scientific reasoning why the compounds of Konings would be expected to react any differently than the compounds of Kirkpatrick. Thus, Applicants' arguments that there is no reasonable expectation of success is not persuasive.

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

10. Claims 34, 53, 54 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kirkpatrick et al. (U.S. Patent 6,552,060) (Filing Date is **August 11, 1998**) and Konings et al. (Konings, D. A. M.; Wyatt, J. R.; Ecker, D. J.; Freier, S. M. "Deconvolution of Combinatorial Libraries for Drug Discovery: Theoretical Comparison of Pooling Strategies" *J. Med. Chem.* **1996**, *39*, 2710-2719) and Fischli et al. (US Patent No. 4,766,133) (Date of Patent is **August 23, 1988**).

For ***claims 34, 53 and 54,*** the combined references of Kirkpatrick et al. and Konings et al. teach all the limitations stated in the 35 U.S.C. 103(a) rejection above (incorporated in its entirety herein by reference), which renders obvious claims 34, 53 and 54.

The combined prior art teachings of Kirkpatrick et al. and Konings et al. differ from the claimed invention as follows:

For ***claim 58***, the combined prior art teachings of Kirkpatrick et al. and Konings et al. differ from the claimed invention by not specifically reciting R^8 = straight chain alkyl with 1-10 carbon atoms substituted with an amine.

However, Fischli et al. teach the following limitations that are deficient in the combined teachings of Kirkpatrick et al. and Konings et al.:

For ***claim 58***, Fischli et al. (see entire document) teach disulfide compounds with R^8 = straight chain alkyl with 1-10 carbon atoms substituted with an amine (e.g., see Fischli et al., column 13, compound G).

It would have been obvious to one skilled in the art at the time the invention was made to use the combinatorial high throughput screening techniques as taught by Kirkpatrick et al. and Konings et al. against thioredoxin reductase/thioredoxin targets (e.g., see Kirkpatrick et al., column 22, paragraph 1; see also column 23, paragraph 1) with the disulfides as taught by Fischli et al. (e.g., see Fischli et al., column 12, compound G) because Kirkpatrick et al. and Konings et al. teach that disulfides with benzimidazole and/or imidazole rings are a preferred embodiment for high throughput screening against thioredoxin reductase/thioredoxin targets (e.g., Kirkpatrick et al., abstract, see especially column 18, lines 24-25), which would encompass the compounds disclosed by Fischli et al. Furthermore, one of ordinary skill in the art would have been motivated to use the compounds disclosed by Fischli et al. because Fischli et al. teach that their disulfides are "gastric acid secretion-inhibiting and/or mucosa-protecting" (e.g., see column 1, lines 66-67), which would be beneficial because Kirkpatrick et al. and Konings et al. teach the therapeutic application of disulfides to the stomach and/or

gastrointestinal tract which would require such protection (see Kirkpatrick et al., "The term 'cancer' refers to ... stomach cancer"; see also column 3, line 39; see also column 8, line 58). Furthermore, one of ordinary skill in the art would have reasonably expected to be successful because all three references teach the application of similar compounds (e.g., all three references teach asymmetric disulfides with heteroaromatic rings).

Response

11. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

Applicants seem to be arguing that the references represent non-analogous art because "Fishchli is completely unrelated to combinatorial chemistry" whereas "Konings is a paper discussing theoretical combinatorial chemistry" and also that the references taken individually or in combinations of two, do not teach all the claimed limitations and thus would not provide a reasonable expectation of success i.e., Applicants argue, "Konings reference discusses theoretical combinatorial chemistry using RNA hybridization s a model and does not discuss asymmetrical disulfides ... Fischli, which is silent on combinatorial chemistry, does not remedy this deficiency to provide the requisite motivation or a reasonable expectation of success " (e.g., 8/24/04 Response, pages 7-8).

This is not found persuasive for the following reasons:

The Examiner respectfully disagrees. In response to applicant's arguments against the Kirkpatrick et al., Konings et al. and/or Fischli et al. references individually and/or in combinations of two, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Here, all of the claimed limitations have been met as set forth in the rejection above. In addition, the references do represent analogous art because either the contain similar compounds (i.e., disulfides), or similar interactions (i.e., ligand/receptor) or similar techniques (i.e., combinatorial), etc. In addition, adequate motivation has been set forth because in addition to the "gastric" argument, the Examiner also has set forth the fact that Konings et al. teach that disulfides with benzimidazole and/or imidazole rings are a "preferred embodiment" for high throughput screening against thioredoxin reductase/thioredoxin targets (e.g., Kirkpatrick et al., abstract, see especially column 18, lines 24-25), which would encompass the compounds disclosed by Fischli, which has not been refuted by Applicants.

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
November 13, 2004